

CLAIMS:

1. A nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a protein or a derivative, homologue, analogue or mimetic thereof or a nucleotide sequence capable of hybridizing thereto under low stringency conditions at 42°C wherein said protein comprises a SOCS box in its C-terminal region.
2. A nucleic acid molecule according to claim 1 wherein the protein further comprises a protein:molecule interacting region.
3. A nucleic acid molecule according to claim 1 wherein the protein:molecule interacting region is located in a region N-terminal of the SOCS box.
4. A nucleic acid molecule according to claim 2 or 3 wherein the protein:molecule interacting region is a protein:DNA binding region or a protein:protein binding region.
5. A nucleic acid molecule according to claim 4 wherein the protein:molecule interacting region is one or more of an SH2 domain, WD-40 repeats or ankyrin repeats.
5. A nucleic acid molecule according to any one of claims 1-5 wherein the SOCS box comprises the amino acid sequence:

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X₁ X₂ X₃ X₄ X₅ X₆ X₇ X₈ X₉ X₁₀ X₁₁ X₁₂ X₁₃ X₁₄ X₁₅ X₁₆ [X₁₇]_n X₁₇ X₁₈ X₁₉ X₂₀
X₂₁ X₂₂ X₂₃ [X₂₄]_n X₂₄ X₂₅ X₂₆ X₂₇ X₂₈

wherein: X₁ is L, I, V, M, A or P;
X₂ is any amino acid residue;
X₃ is P, T or S;
X₄ is L, I, V, M, A or P;
X₅ is any amino acid;
X₆ is any amino acid;

X₇ is L, I, V, M, A, F, Y or W;

X₈ is C, T or S;

X₉ is R, K or H;

X₁₀ is any amino acid;

X₁₁ is any amino acid;

X₁₂ is L, I, V, M, A or P;

X₁₃ is any amino acid;

X₁₄ is any amino acid;

X₁₅ is any amino acid;

X₁₆ is L, I, V, M, A, P, G, C, T or S;

[X_j]_n is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X_j may comprise the same or different amino acids selected from any amino acid residue;

X₁₇ is L, I, V, M, A or P;

X₁₈ is any amino acid;

X₁₉ is any amino acid;

X₂₀ is L, I, V, M, A or P;

X₂₁ is P;

X₂₂ is L, I, V, M, A, P or G;

X₂₃ is P or N;

[X_j]_n is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X_j may comprise the same or different amino acids selected from any amino acid residue;

X₂₄ is L, I, V, M, A or P;

X₂₅ is any amino acid;

X₂₆ is any amino acid;

X₂₇ is Y or F, and

X₂₈ is L, I, V, M, A or P.

5 7. A nucleic acid molecule according to claim 6 wherein the protein modulates signal transduction.

5 8. A nucleic acid molecule according to claim 7 wherein the signal transduction is modulated by a cytokine or a hormone, a microbe or a microbial product, a parasite, an antigen or other effector molecule.

5 9. A nucleic acid molecule according to claim 8 wherein the protein modulates cytokine-mediated signal transduction.

5 10. A nucleic acid molecule according to claim 9 wherein the signal transduction is mediated by one or more of the cytokines EPO, TPO, G-CSF, GM-CSF, IL-3, IL-2, IL-4, IL-7, IL-13, IL-6, LIF, IL-12, IFN γ , TNF α , IL-1 and/or M-CSF.

5 11. A nucleic acid molecule according to claim 10 wherein the signal transduction is mediated by one or more of IL-6, LIF, OSM, IFN- γ and/or thrombopoietin.

5 12. A nucleic acid molecule according to claim 11 wherein the signal transduction is mediated by IL-6.

13. A nucleic acid molecule according to claim 1 wherein the nucleotide sequence encodes an amino acid sequence substantially as set forth in SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 18, SEQ ID NO. 21, SEQ ID NO. 25, SEQ ID NO. 29, SEQ ID NO. 36, SEQ ID NO. 41, SEQ ID NO. 44, SEQ ID NO. 46 or SEQ ID NO. 48 or an amino acid sequence having at least about 15% similarity to all or part of the listed sequences or a nucleotide sequence which hybridizes to the nucleic acid molecule under low stringency conditions at 42°C.

14. A nucleic acid molecule according to claim 1 wherein the nucleotide sequence is substantially as set forth in SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ

ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 45 or SEQ ID NO. 47 or a nucleotide sequence having at least 15% similarity to all or a part of the listed sequences or a nucleotide sequence capable of hybridizing to the listed sequences under low stringency conditions at 42°C.

15. A nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a protein or a derivative, homologue, analogue or mimetic thereto or a nucleotide sequence capable of hybridizing thereto under low stringency conditions at 42°C wherein said protein exhibits the following characteristics:

(i) comprises a SOCS box in its C-terminal region wherein said SOCS box comprises the amino acid sequence:

$X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} [X_{17}]_n X_{18} X_{19} X_{20}$
 $X_{21} X_{22} X_{23} [X_{24}]_n X_{25} X_{26} X_{27} X_{28}$

wherein:

- X_1 is L, I, V, M, A or P;
- X_2 is any amino acid residue;
- X_3 is P, T or S;
- X_4 is L, I, V, M, A or P;
- X_5 is any amino acid;
- X_6 is any amino acid;
- X_7 is L, I, V, M, A, F, Y or W;
- X_8 is C, T or S;
- X_9 is R, K or H;
- X_{10} is any amino acid;
- X_{11} is any amino acid;
- X_{12} is L, I, V, M, A or P;
- X_{13} is any amino acid;
- X_{14} is any amino acid;
- X_{15} is any amino acid;
- X_{16} is L, I, V, M, A, P, G, C, T or S;

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$[X]_n$ is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X_i may comprise the same or different amino acids selected from any amino acid residue;

X_{17} is L, I, V, M, A or P;

X_{18} is any amino acid;

X_{19} is any amino acid;

X_{20} L, I, V, M, A or P;

X_{21} is P;

X_{22} is L, I, V, M, A, P or G;

X_{23} is P or N;

$[X]_n$ is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X_i may comprise the same or different amino acids selected from any amino acid residue;

X_{24} is L, I, V, M, A or P;

X_{25} is any amino acid;

X_{26} is any amino acid;

X_{27} is Y or F;

X_{28} is L, I, V, M, A or P; and

- (ii) comprises at least one of an SH2 domain, WD-40 repeats and/or ankyrin repeats or other protein:molecule interacting domain in a region N-terminal of the SOCS box; and
- (iii) modulates signal transduction.

16. An isolated protein or a derivative, homologue or mimetic thereof comprising a SOCS box in its C-terminal region.

17. An isolated protein according to claim 16 wherein the protein further comprises a protein:molecule interacting region.

18. An isolated protein according to claim 17 wherein the protein:molecule interacting region is located in a region N-terminal of the SOCS box.

2 19. An isolated protein according to claim 16 or 17 wherein the protein:molecule interacting region is a protein:DNA binding region or a protein:protein binding region.

2 20. An isolated protein according to claim 19 wherein the protein:molecule interacting region is one or more of an SH2 domain, WD-40 repeats or ankyrin repeats.

4 21. An isolated protein according to any one of claims 16-20 wherein the SOCS box comprises the amino acid sequence:

X₁ X₂ X₃ X₄ X₅ X₆ X₇ X₈ X₉ X₁₀ X₁₁ X₁₂ X₁₃ X₁₄ X₁₅ X₁₆ [X₁₇]_n X₁₈ X₁₉ X₂₀
 X₂₁ X₂₂ X₂₃ [X₂₄]_n X₂₅ X₂₆ X₂₇ X₂₈

wherein:

- X₁ is L, I, V, M, A or P;
- X₂ is any amino acid residue;
- X₃ is P, T or S;
- X₄ is L, I, V, M, A or P;
- X₅ is any amino acid;
- X₆ is any amino acid;
- X₇ is L, I, V, M, A, F, Y or W;
- X₈ is C, T or S;
- X₉ is R, K or H;
- X₁₀ is any amino acid;
- X₁₁ is any amino acid;
- X₁₂ is L, I, V, M, A or P;
- X₁₃ is any amino acid;
- X₁₄ is any amino acid;
- X₁₅ is any amino acid;
- X₁₆ is L, I, V, M, A, P, G, C, T or S;
- [X₁₇]_n is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X₁₇ may comprise the same or different amino acids selected from any amino acid residue;

X_{11} is L, I, V, M, A or P;

X_{18} is any amino acid;

X_{19} is any amino acid;

X_{20} L, I, V, M, A or P;

X_{21} is P;

X_{22} is L, I, V, M, A, P or G;

X_{23} is P or N;

$[X_j]_n$ is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X_j may comprise the same or different amino acids selected from any amino acid residue;

X_{24} is L, I, V, M, A or P;

X_{25} is any amino acid;

X_{26} is any amino acid;

X_{27} is Y or F; and

X_{28} is L, I, V, M, A or P.

4 22. An isolated protein according to claim 21 wherein the protein modulates signal transduction.

4 23. An isolated protein according to claim 22 wherein the signal transduction is modulated by a cytokine or other endogenous molecule, a hormone, a microbe or a microbial product, a parasite, an antigen or other effector molecule.

4 24. An isolated protein according to claim 23 wherein the protein modulates cytokine-mediated signal transduction.

4 25. An isolated protein according to claim 24 wherein the signal transduction is mediated by one or more of the cytokines EPO, TPO, G-CSF, GM-CSF, IL-3, IL-2, IL-4, IL-7, IL-13, IL-6, LIF, IL-12, IFN γ , TNF α , IL-1 and/or M-CSF.

4 26. An isolated protein according to claim 25 wherein the signal transduction is mediated by

one or more of IL-6, LIF, OSM, IFN- γ and/or thrombopoietin.

4 27. An isolated protein according to claim 26 wherein the signal transduction is mediated by IL-6.

28. An isolated protein according to claim 16 wherein said protein comprises an amino acid sequence substantially as set forth in SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 18, SEQ ID NO. 21, SEQ ID NO. 25, SEQ ID NO. 29, SEQ ID NO. 36, SEQ ID NO. 41, SEQ ID NO. 44, SEQ ID NO. 46 or SEQ ID NO. 48 or an amino acid sequence having at least about 15% similarity to all or part of the listed sequences.

29. An isolated protein according to claim 16 wherein the said protein is encoded by a nucleotide sequence substantially as set forth in SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 45 or SEQ ID NO. 47 or a nucleotide sequence having at least 15% similarity to all or a part of the listed sequences or a nucleotide sequence capable of hybridizing to the listed sequences under low stringency conditions at 42°C.

30. An isolated protein or a derivative, homologue, analogue or mimetic thereof having the following characteristics:

(i) comprises a SOCS box in its C-terminal region wherein said SOCS box comprises the amino acid sequence:

X₁ X₂ X₃ X₄ X₅ X₆ X₇ X₈ X₉ X₁₀ X₁₁ X₁₂ X₁₃ X₁₄ X₁₅ X₁₆ [X_i]_n X₁₇ X₁₈ X₁₉ X₂₀
X₂₁ X₂₂ X₂₃ [X_j]_n X₂₄ X₂₅ X₂₆ X₂₇ X₂₈

wherein: X_i is L, I, V, M, A or P;

X_2 is any amino acid residue;

X_3 is P, T or S;

X_4 is L, I, V, M, A or P;

X_5 is any amino acid;

X_6 is any amino acid;

X_7 is L, I, V, M, A, F, Y or W;

X_8 is C, T or S;

X_9 is R, K or H;

X_{10} is any amino acid;

X_{11} is any amino acid;

X_{12} is L, I, V, M, A or P;

X_{13} is any amino acid;

X_{14} is any amino acid;

X_{15} is any amino acid;

X_{16} is L, I, V, M, A, P, G, C, T or S;

$[X_i]_n$ is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X_i may comprise the same or different amino acids selected from any amino acid residue;

X_{17} is L, I, V, M, A or P;

X_{18} is any amino acid;

X_{19} is any amino acid;

X_{20} L, I, V, M, A or P;

X_{21} is P;

X_{22} is L, I, V, M, A, P or G;

X_{23} is P or N;

$[X_i]_n$ is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X_i may comprise the same or different amino acids selected from any amino acid residue;

X_{24} is L, I, V, M, A or P;

X_{25} is any amino acid;

X_{26} is any amino acid;

X_{27} is Y or F;

X_{28} is L, I, V, M, A or P; and

- (ii) comprises at least one of an SH2 domain, WD-40 repeats and/or ankyrin repeats or other protein:molecule interacting domain in a region N-terminal of the SOCS box; and
- (iii) modulates signal transduction.

31. A method of modulating levels of a SOCS protein in a cell said method comprising contacting a cell containing a SOCS gene with an effective amount of a modulator of SOCS gene expression or SOCS protein activity for a time and under conditions sufficient to modulate levels of said SOCS protein.
32. A method of modulating signal transduction in a cell containing a SOCS gene comprising contacting said cell with an effective amount of a modulator of SOCS gene expression or SOCS protein activity for a time sufficient to modulate signal transduction.
33. A method of influencing interaction between cells wherein at least one cell carries a SOCS gene, said method comprising contacting the cell carrying the SOCS gene with an effective amount of a modulator of SOCS gene expression or SOCS protein activity for a time sufficient to modulate signal transduction.
34. A method according to any one of claims 31-33 wherein signal transduction is mediated by a cytokine, a hormone, a microbe or a microbial product, a parasite, an antigen or other effector molecule.
35. A method according to claim 34 wherein the cytokine is one or more of EPO, TPO, G-CSF, GM-CSF, IL-3, IL-2, IL-4, IL-7, IL-13, IL-6, LIF, IL-12, IFN γ , TNF α , IL-1 and/or M-CSF.
36. A method according to claim 35 wherein the cytokine is one or more of IL-6, LIF, OSM, IFN- γ and/or thrombopoietin.

37. A method according to claim 36 wherein the cytokine is IL-6.

38. A method according to any one of claims 31-37 wherein the SOCS gene encodes a protein having a SOCS box comprising the amino acid sequence:

$X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} [X_n]_n X_{17} X_{18} X_{19} X_{20}$
 $X_{21} X_{22} X_{23} [X_n]_n X_{24} X_{25} X_{26} X_{27} X_{28}$

wherein:

- X_1 is L, I, V, M, A or P;
- X_2 is any amino acid residue;
- X_3 is P, T or S;
- X_4 is L, I, V, M, A or P;
- X_5 is any amino acid;
- X_6 is any amino acid;
- X_7 is L, I, V, M, A, F, Y or W;
- X_8 is C, T or S;
- X_9 is R, K or H;
- X_{10} is any amino acid;
- X_{11} is any amino acid;
- X_{12} is L, I, V, M, A or P;
- X_{13} is any amino acid;
- X_{14} is any amino acid;
- X_{15} is any amino acid;
- X_{16} is L, I, V, M, A, P, G, C, T or S;
- $[X_n]_n$ is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X_n may comprise the same or different amino acids selected from any amino acid residue;
- X_{17} is L, I, V, M, A or P;
- X_{18} is any amino acid;
- X_{19} is any amino acid;
- X_{20} is L, I, V, M, A or P;
- X_{21} is P;

X_2 is L, I, V, M, A, P or G;

X_{23} is P or N;

[X]_n is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X_n may comprise the same or different amino acids selected from any amino acid residue;

X_{ij} is L, I, V, M, A or P;

X_{25} is any amino acid;

X_{26} is any amino acid;

~~X₂₇~~ is Y or F; and

X₂₈ is L, I, V, M, A or P.

39. A method according to claim 38 wherein the SOCS gene comprises a nucleotide sequence selected from SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 45 or SEQ ID NO. 47.

40. A method according to claim 38 wherein the SOCS gene encodes a protein comprising an amino acid sequence substantially as set forth in SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 18, SEQ ID NO. 21, SEQ ID NO. 25, SEQ ID NO. 29, SEQ ID NO. 36, SEQ ID NO. 41, SEQ ID NO. 44, SEQ ID NO. 46 or SEQ ID NO. 48.

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